REMARKS

A. THE AMENDMENTS TO THE CLAIMS

Claims 1-19, 26-36, and 45-61 are pending. Claims 26-36 and 45-61 are withdrawn from consideration, and claims 1-19 are currently under examination insofar as the claims read on an anti-NF-κB inducing kinase (NIK) antibody that binds SEQ ID NOs: 5, 6, or 3.

Claims 1 and 14 have been amended to recite that the antibody or fragment thereof is capable of specifically binding the amino acid sequence set forth in SEQ ID NO: 5, SEQ ID NO: 6, and/or SEQ ID NO: 3, wherein the amino acid sequence comprises a phosphorylated threonine at amino acid position 559 of SEQ ID NO: 5. Claims 2-11 and 19 have been amended to refer to an antibody or fragment thereof. Claims 5 and 18 were amended to remove reference to "a CDR." Claim 17 was amended to characterize the antibody or antibody fragment as a polyclonal, monoclonal, chimeric, humanized, or anti-anti-idiotype antibody or fragment thereof from murine origin. The amendments to the claims are fully supported by the specification at, e.g., page 11, lines 24-30; page 14, lines 26-31; page 15, lines 7-11 and 19-24; page 16, lines 13-15; and page 31, lines 14-17. No new matter has been added by way of the amendments.

B. THE OFFICE ACTION

The Office rejected claim 17 under 35 U.S.C. § 112, second paragraph, for assertedly being indefinite. Claims 1-14 and 16-19 were rejected under 35 U.S.C. § 112, first paragraph, for assertedly lacking enablement. The Office also rejected claims 1-4, 6-10, 12, 14-16, and 19 under 35 U.S.C. § 102(e) for assertedly being anticipated by U.S. Patent No. 6,822,138 ("Schreiber"). Claims 1-10, 12, and 14-19 also were rejected under 35 U.S.C. § 103 for assertedly being obvious in view of Schreiber, Lin et al., *Mol. Cell Biol, 18*(10), 5899-5907 (1998) ("Lin"); Campbell, *Monoclonal Antibody Technology*, Chapter 1, pp. 1-32 (1984) ("Campbell"); Green, *JIM*, 231, 11-23 (1999) ("Green"); and Owens et al., *JIM*, 168, 149-165 (1994) ("Owens"). Reconsideration of the rejections is respectfully requested.

C. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN.

The Office rejected claim 17 for assertedly being indefinite. The Office asserted that, because claim 14 recites that the antibody or fragment thereof is a human antibody, it is not clear whether the claimed antibody is human or murine. Applicants respectfully disagree. Solely in an effort to advance prosecution, however, claim 17 has been amended to characterize the antibody or antibody fragment as a polyclonal, monoclonal, chimeric, humanized, or anti-anti-idiotype antibody or fragment thereof from murine origin. One of ordinary skill in the art can recognize the metes and bounds of the claims, and the rejection under Section 112, second paragraph, should be withdrawn.

D. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN.

Claims 1-14 and 16-19 were rejected under Section 112, first paragraph, for assertedly lacking enablement. The rejection is respectfully traversed for the reasons set forth below.

The Office raised three issues with respect to the enablement of claims 1-14 and 16-19. First, with respect to claims 5 and 18, the Office asserted that the specification does not reasonably provide enablement for an antibody fragment consisting of fewer than six complementary determining regions (CDRs). Claims 5 and 18 have been amended to delete reference "a CDR," thereby rendering the rejection moot.

Second, the Office requested Applicants' assurance that restrictions on the availability of hybridoma NIK-P4 30.12 deposited with the Collection Nationale de Culture de Microorganismes (CNCM) will be removed upon the grant of a U.S. patent. In accordance with 37 C.F.R. § 1.808, the depositor's restrictions on the availability of the deposited material will be removed upon the granting of the patent.

Finally, the Office rejected claims 1-12, 14, and 16-19 because the specification assertedly does not enable the making or using of an antibody that binds to "any" amino acid or portion of SEQ ID NOs: 3, 5, 6 while retaining the ability to detect NIK or a mutein, functional derivative, active fraction, circularly permutated derivative, salt, or a

portion of NIK. In particular, the Office asserted that the claims encompass antibodies that bind to as few as two amino acids of SEQ ID NO: 5 and variants of SEQ ID NOs: 5, 6, and 3, while only antibodies that bind to the amino acid sequences set forth in SEQ ID NOs: 5, 6, and 3 have been reduced to practice.

While Applicants disagree with the Office's assertions, claims 1 and 14 have been amended solely in an effort to advance prosecution of the instant application to recite that the antibody or fragment thereof is capable of specifically binding the amino acid sequence set forth in SEQ ID NO: 5, SEQ ID NO: 6, and/or SEQ ID NO: 3, wherein the amino acid sequence comprises a phosphorylated threonine at amino acid position 559 of SEQ ID NO: 5. The breadth of the genus of antibodies encompassed by the proposed claim is not unlimited; the antibody or fragment thereof binds to the NIK protein amino acid sequence comprising phosphorylated T559 referenced in the claims. The specification fully enables the anti-NIK antibodies or fragments thereof encompassed by the claims.

Having the phosphorylated NIK protein or protein fragment in hand, one of ordinary skill in the art had the requisite skill to generate anti-NIK antibodies using the specification as a guide. For example, the specification describes how to obtain antibodies by immunizing a mammal with a target antigen and isolating antibodies with desired binding specificity at, e.g., page 20, line 29, through page 21, line 4; page 22, lines 3-12; page 22, line 24, through page 23, line 25; page 41, line 29, through page 42, line 15; and page 67, line 25, through page 69, line 6. Materials and methods for generating monoclonal antibodies are described in the specification at, e.g., page 30, lines 15-24, and page 67, line 25, through page 69, line 6. Methods for recombinantly producing an antibody or antibody fragment using, for example, phage display, are provided at page 28, line 29, through page 30, line 7. The specification also teaches exemplary methods for producing antibody fragments at, e.g., page 27, line 29, through page 28, line 20. In addition, Applicants describe an exemplary monoclonal antibody that binds SEQ ID NO: 3, is specific for phosphorylated NIK, and inhibits NIK activation (see, e.g., page 18, lines 17-19; and page 70, line 1, through page 72, line 4).

The guidance provided by Applicants is sufficient to allow an ordinary researcher, in 2005, to generate an anti-NIK antibody or fragment thereof having the recited activity without undue experimentation. One of ordinary skill in the art could make anti-NIK

antibody and antibody fragment candidates, and screen candidates for binding to phosphorylated NIK or a mutein, functional derivative, active fraction, circularly permutated derivative, salt, or a portion thereof using routine laboratory methods, such as those described in the specification at, e.g., page 22, line 24, through page 24, line 23. Screening even a large number of candidates does not constitute undue experimentation where, as in this instance, the disclosure provides direction and guidance on how to practice the invention. *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.); *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988). In fact, the *In re Wands* court addressed such a factual issue and concluded that antibody-based screening did not involve a quantity of experimentation supporting a conclusion that the experimentation was undue.

The Office further asserted that one of ordinary skill would not have been able to use the antibody that binds SEQ ID NOs: 5, 6, or 3 to detect all NIK variants or a NIK fragment, mutein, functional derivative, active fraction, circularly permutated derivative, or salt. According to the Office, even slight alterations in target protein structure may abrogate antibody binding and, therefore, an antibody that binds SEQ ID NOs: 5, 6, or 3 will not bind all variants of the peptides. The alleged presence of inoperative embodiments, however, does not render a claim non-enabled when one of ordinary skill could identify operative embodiments "with expenditure of no more effort than is normally required in the art." M.P.E.P. § 2164.08(b). Here, the ordinary practitioner need only use routine screening techniques, such as those described in the specification at, e.g., page 22, line 24, through page 24, line 23; and page 69, line 10, through page 75, line 27, to identify anti-NIK antibodies that bind a particular NIK variant. Routine screening does not constitute undue experimentation.

Additionally, the Office improperly picked one of the many uses disclosed in the application for the claimed antibody, and rejected the claims for not being enabled with respect to that particular use. The claimed antibody is not limited to a particular use in the

pending claims and, therefore, any enabled use that reasonably correlates with the scope of the pending claims is sufficient to satisfy Section 112, first paragraph. See M.P.E.P. § 2164.01(c) ("If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." (Emphasis added.)).

The specification teaches multiple exemplary uses for the claimed antibody and composition including, but not limited to, regulating the biochemical activity of NIK (e.g., regulating NIK kinase activity); purifying or detecting phosphorylated NIK; purifying or detecting a NIK fragment, mutein, functional derivative, active fraction, circularly permutated derivative, or salt; and identifying a ligand capable of inducing NFκB activation (see, e.g., page 9, lines 24-32; page 10, lines 18-31; page 18, lines 6-14; page 21, lines 16-29; page 22, lines 13-23; page 23, line 26, through page 24, line 4; page 35, line 4, through page 37, line 15; and page 70, line 21, through page 71, line 9). The rejection failed to explain how *each* of the disclosed uses was not enabled by the specification. That failure is unsurprising because the specification provides sufficient guidance to enable one of ordinary skill to use the claimed antibody. For instance, the specification teaches how to use the claimed anti-NIK antibody to regulate the biochemical activity of NIK. In Examples 4 and 5, cells were exposed to CD70 or CD40 ligand in combination with NIK-P4 30.12 antibody, an antibody that specifically binds SEQ ID NO: 3. The anti-NIK antibody blocked CD70- and CD40-mediated IκB degradation, thereby inhibiting NIK-mediated NFκB activation. NFκB is known as an important regulator of expression of pro-inflammatory genes and one of skill would understand that the anti-NIK antibody would inhibit NIK-induced inflammation. The teaching of the specification is sufficient to satisfy the "use" requirement of Section 112, first paragraph.

The specification enables the full scope of claims 1-14 and 16-19, and the rejection under Section 112, first paragraph, should be withdrawn.

E. THE REJECTION UNDER 35 U.S.C. § 102(E) SHOULD BE WITHDRAWN.

Claims 1-4, 6-10, 12, 14-16, and 19 were rejected under 35 U.S.C. § 102(e) for assertedly being anticipated by Schreiber. The rejection is respectfully traversed for the reasons set forth below.

Schreiber anticipates the pending claims only if the reference teaches each and every element of the pending claims. See, e.g., *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631 (Fed. Cir. 1987). Claims 1-4, 6-10, 12, 14-16, and 19 are directed to a polyclonal, monoclonal, chimeric, humanized, human or anti-anti-idiotype antibody or fragment thereof (or a pharmaceutical composition comprising the antibody or fragment thereof) capable of specifically binding an amino acid sequence set forth in SEQ ID NOs: 5, 6, or 3 comprising a phosphorylated threonine at amino acid position 559 of SEQ ID NO: 5. Schreiber discloses a genus of antibodies that bind NIK, and does not teach each and every feature of the instant antibody or antibody fragment that selectively binds NIK protein comprising phosphorylated T559, as recited in the pending claims. It is well-settled that disclosure of a genus does not anticipate a claimed species. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category"). Indeed, the reference does not teach or suggest the specific portion of NIK to which the claimed antibody binds, nor does the reference teach a subset of antibodies that specifically binds a phosphorylated NIK.

Despite the failure of Schreiber to teach each and every element of any of the pending claims, the Office asserted that Applicants must prove that the described genus of polyclonal antibodies would not bind to the recited NIK fragments, suggesting that the disclosed genus of antibodies inherently meets the limitations of the pending claims. To rely on a theory of inherency, however, the Office must provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Interf. 1990). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citations omitted). The Office failed to present evidence or reasoning showing

that any prior art antibodies would necessarily bind to portions of NIK containing phosphorylated T559 as recited in the claims and, therefore, has not met the Office's burden. Without such evidence or reasoning, the Office cannot require an applicant to prove that the prior art does not possess the claimed characteristic. See *Ex parte Jurg Zimmerman* 2003 WL 25277881, *4 (Bd. Pat. App. & Interf. 2003), quoting *Ex parte Skinner*, 2 U.S.P.Q.2d 1788 (Bd. Pat. App. & Interf. 1986).

Additionally, Applicants' specification provides evidence that not all polyclonal anti-NIK antibodies specifically bind the phosphorylated version of NIK. See Example 1 of the specification, which reports results of a binding assay using polyclonal antibodies raised against NIK fragments. As explained at page 68, lines 8-27, polyclonal antibodies raised against NIK activation loop fragments comprising phosphorylated T559 did not elicit antibodies that specifically bind NIK comprising phosphorylated T559. Accordingly, Applicants have shown that features of the claimed antibodies are not necessarily found in the genus of anti-NIK antibodies of Schreiber. The reference fails to explicitly or inherently disclose the particular anti-NIK antibodies of the pending claims. Therefore, the rejection of claims 1-4, 6-10, 12, 14-16, and 19 under 35 U.S.C. § 102(e) over Schreiber is improper and should be withdrawn.

F. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN.

The Office rejected claims 1-10, 12, and 14-19 under Section 103 for assertedly being obvious in view of Schreiber, Lin, Campbell, Green, and Owens. The rejection is respectfully traversed.

Schreiber does not disclose an antibody that selectively binds NIK protein comprising phosphorylated T559. Lin purportedly teaches that substitution of threonine at position 559 of SEQ ID NO: 5 abolishes NIK activity, and the Office asserted that it would have been obvious to one of ordinary skill to make an antibody that would bind to the NIK activation loop containing phosphorylated T559 to block NIK's activation site. However, modification of the Schreiber teaching to generate an antibody or antibody fragment that specifically binds NIK or a portion thereof comprising phosphorylated T559 was unpredictable prior to the instant invention. As explained above, the specification provides

evidence that not all antibodies raised against the activation loop specifically bind the region of NIK comprising phosphorylated T559. In Example 1, polyclonal antibodies were generated using as immunogens three fragments of the NIK activation loop comprising amino acids 553-566, amino acids 553-562, or amino acids 549-560. All of the immunogenic fragments comprised phosphorylated T559. However, only the fragment comprising amino acids 549-560 produced antibodies specific to phosphorylated NIK. Neither of the cited references provides a predictable basis for generating an anti-NIK antibody as currently claimed. The remaining secondary references, Campbell, Green and Owens, were cited as purportedly describing human, humanized, and chimeric antibodies or providing motivation for generating monoclonal antibodies, and fail to cure the deficiencies of Schreiber and Lin in rendering the invention obvious. Accordingly, the Section 103 rejection should be withdrawn.

G. CONCLUSION

Applicants submit that the pending application is in condition for allowance. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions concerning this submission that might be efficiently resolved in that manner.

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Respectfully submitted,

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